found inter alia in the specification, as originally filed, on page 24, lines 7-10. Support for amended claim 16 may be found inter alia in the specification, as originally filed, on page 20, line 13 through page 22, line 30. Support for amended claims 22 and 29 may be found inter alia in the specification, as originally filed, on page 26, lines 4-12. Support for amended claim 30 may be found inter alia in the specification, as originally filed, on page 30, line 5 through page 33, line 1. Support for amended claims 32-34 and 36 may be found inter alia in the specification, as originally filed, on page 33, line 1 through page 34, line 1.

Rejection Under 35 U.S.C. §102(b)

On page 3 of the Office Action, the Examiner rejected claims 1-5, 22, 26-30, and 32 under 35 U.S.C. §102(b) as being anticipated by Wu, et al. The Examiner alleged that the Wu reference also teaches phenyl substituted azaspiro piperizine compounds that fall within the genus of the compounds as instantly claimed, specifically where, Y and Z are C(=O); R_1 and R_2 form a ring; X is N; R_3-R_8 are H; R_9-R_{13} are H, CH_3, OCH_3, Cl, etc. The Examiner referred to table IA and IB on page 877. The Examiner further alleged that Wu teaches that these compounds are useful to antagonize amphetamine aggregation, which is inherently related to the adrenergic system and that providing the same host, mammal, with the same drug would inherently treat and inhibit the same disease and receptor as is instantly claimed.

In an attempt to advance the prosecution of the subject application, but without conceding the correctness of the Examiner's position, applicants have canceled claim 1 and 5, and have amended claims 22, 29-30, and 32 to be dependent on claim 16, which has been rewritten in independent form.

Applicants respectively maintain the claims 2-4 are not anticipated by Wu, et al.

In support of this statement, applicants enclose herewith as **Exhibit B** a Declaration of Dr. Michael Konkel pursuant to 37 C.F.R. §1.132 ("THE KONKEL DECLARATION"). Applicants submit this Declaration as evidence that claims 2-4 directed to methods of inhibiting activation of a human α_{1d} adrenergic receptor with selectivity over the human α_{1b}, α_{1a} and $5HT_{1A}$ receptors are not anticipated by Wu, Y.-H. et al., "Psychosedative Agents. N-(4-Phenyl-1-piperazinylalkyl)-substituted cyclic imides" *J. Med. Chem.* (1969) 12: 876-881.

Dr. Konkel notes in his Declaration that the use of the compounds disclosed by Wu, et al. would not fall within the scope of claims 2-4, as amended. Specifically, the selectivity of Wu's compounds, which bind to a α_{1d} receptor relative to the $5HT_{1a}$ receptor, does not exceed 10-fold.

In light of Dr. Konkel's Declaration, the use of the compounds disclosed by Wu, et al. would not fall within the scope of claims 2-4, as amended. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Rejection Under 35 U.S.C. §103(a)

On page 4 of the Office Action, the Examiner rejected claims 6 and 13-15 under 35 U.S.C. §103(a) as being unpatentable under Wu, et al. The Examiner alleged that applicants claim phenyl substituted azaspiro piperizine compounds according to the formula in claim 1, their pharmaceutical compositions and

their corresponding methods of use.

The Examiner alleged that the Wu, et al reference also teaches phenyl substituted azaspiro piperizine compounds that fall within the genus of the compounds as instantly claimed, specficially where, Y and Z are C(=O); R_1 and R_2 form a ring; X is N; R_3-R_8 is H; R_9-R_{13} are H, CH_3, OCH_3, Cl, etc. The Examiner directed applicants attention to Table IA and IB on page 877 of the reference.

The Examiner alleged that the difference between the prior art and the instant claims is that the instant claims have a fluorine instead of a chlorine at the R_9 position.

The Examiner alleged it would have been prima facie obvious for one of ordinary skill in the art at the time of the filing of the instant application to substitute a fluorine for a chlorine on the compounds because to one skilled in the art, fluorine and chlorine are considered analogues or isologues of each other and thus would be expected to have the same or similar activity. The Examiner referred to Ex parte Wisemen, 98 USPQ 277 (1953), in which it was held that compounds are rejected over prior art when the difference between the claimed compounds and the compounds of the prior art is two fluorine atoms versus chlorine atoms. The Examiner said that the basis of this reasoning is that fluorine and chlorine are both halogen elements from the seventh group of the periodic system and the claimed compound is thus an analogue or an isologue of that disclosed in the prior art. The Examiner also alleged that compounds are expected to possess similar properties differing only in degree.

In response, in an attempt to advance the prosecution of the

subject application, but without conceding the correctness of the Examiner's position, applicants have canceled claim 6 and 13 and have amended claims 14 and 15 to be dependent on claim 7, as amended. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

If a telephone conference would be of assistance in advancing prosecution of the subject application, applicants undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed fee of $55.00 for a one-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Assistant Commissioner for Patents, Washington, D.C. 20231.

12/27/02
John P. White Date
Reg. No. 28,678

John P. White
Registration No. 28,678
Attorney for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

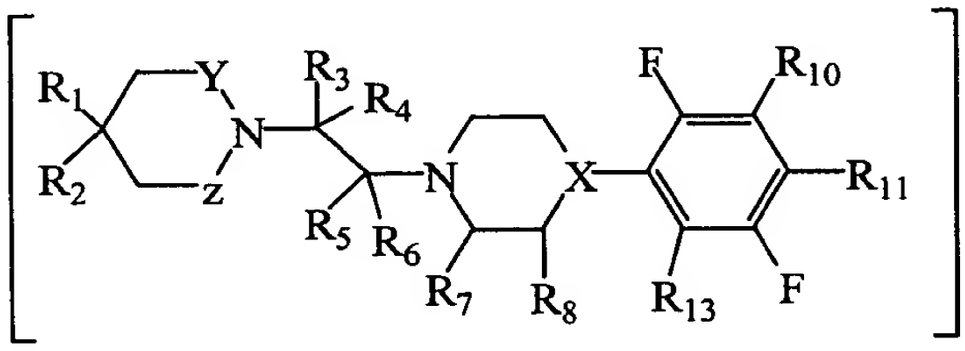
John Haberman
attorney working on case

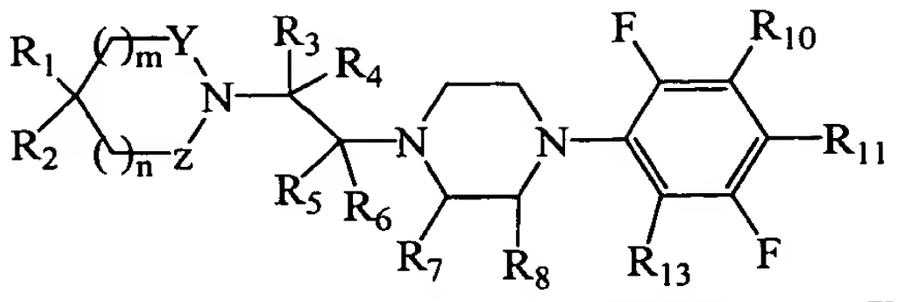
Marked-Up Version of Amendments

Additions are indicated by underlining; deletions are indicated by brackets.

--2. (Amended) A method of inhibiting activation of a human α_{1d} adrenergic receptor which comprises contacting the receptor with a compound so as to inhibit activation of the receptor, wherein the compound binds to the human α_{1d} adrenergic receptor with a binding affinity which is at least 25-fold higher than the binding affinity with which [The method of claim 1, wherein] the compound binds to (i) a human α_{1a} adrenergic receptor and (ii) a human α_{1b} adrenergic receptor, and the compound binds to the human α_{1d} adrenergic receptor with a binding affinity which is at least ten-fold higher than the binding affinity with which the compound binds to a human 5-HT_{1a} receptor.--

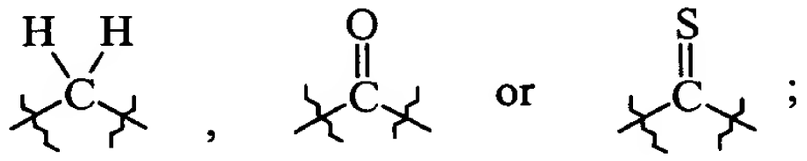
--7. (Amended) A method of inhibiting activation of a human α_{1d} adrenergic receptor which comprises contacting the receptor with a compound so as to inhibit activation of the receptor [The method of claim 6], wherein the compound has the structure:





wherein each m and n is independently an integer from 0 to 2;

wherein each Y and Z is independently



wherein R_1 and R_2 (i) are independently H, branched or unbranched C_1-C_6 alkyl or alkoxy, branched or unbranched C_2-C_6 alkenyl or alkynyl, branched or unbranched C_1-C_6 hydroxyalkyl, hydroxy, substituted or unsubstituted aryl or aryl-(C_1-C_6)-alkyl, or substituted or unsubstituted heteroaryl or heteroaryl-(C_1-C_6)-alkyl, wherein the substituent if present is a halogen, CN, nitro, hydroxy, branched or unbranched C_1-C_6 alkyl or alkoxy group, or branched or unbranched C_2-C_6 alkenyl or alkynyl group; or (ii) taken together form a substituted or unsubstituted cycloalkyl ring containing 3-10 carbons, wherein the substituent if present is a branched or unbranched C_1-C_6 alkyl group or branched or unbranched C_2-C_6 alkenyl or alkynyl group;

wherein R_3 is H, branched or unbranched C_1-C_6 alkyl, branched or unbranched C_2-C_6 alkenyl or alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkylalkyl, aryl, heteroaryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl, substituted C_1-C_6 alkyl, substituted C_3-C_7 cycloalkyl, substituted aryl,

substituted heteroaryl, substituted aryl-(C_1-C_6)-alkyl, or substituted heteroaryl-(C_1-C_6)-alkyl, wherein the substituent if present is a halogen, CN, nitro, C_1-C_6 alkyl, OR_{14}, SR_{14}, $N(R_{14})_2$, $SO_2N(R_{14})_2$, CO_2R_{14}, SO_3R_{14}, $N(R_{14})COR_{14}$, $CON(R_{14})_2$, or $N(R_{14})CON(R_{14})_2$;

wherein R_4 is H or CH_3;

wherein R_5 is H, branched or unbranched C_1-C_6 alkyl, branched or unbranched C_2-C_6 alkenyl or alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkylalkyl, aryl, heteroaryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl, substituted C_1-C_6 alkyl, substituted C_3-C_7 cycloalkyl, substituted aryl, substituted heteroaryl, substituted aryl-(C_1-C_6)-alkyl, or substituted heteroaryl-(C_1-C_6)-alkyl, wherein the substituent if present is a halogen, CN, nitro, C_1-C_6 alkyl, OR_{14}, SR_{14}, $N(R_{14})_2$, $SO_2N(R_{14})_2$, CO_2R_{14}, SO_3R_{14}, $N(R_{14})COR_{14}$, $CON(R_{14})_2$, or $N(R_{14})CON(R_{14})_2$;

wherein R_6 is H, branched or unbranched C_1-C_6 alkyl, branched or unbranched C_2-C_6 alkenyl or alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkylalkyl, aryl, heteroaryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl, substituted C_1-C_6 alkyl, substituted C_3-C_7 cycloalkyl, substituted aryl, substituted heteroaryl, substituted aryl-(C_1-C_6)-alkyl, or substituted heteroaryl-(C_1-C_6)-alkyl, wherein the substituent if present is a halogen, CN, nitro, C_1-C_6 alkyl, OR_{14}, SR_{14}, $N(R_{14})_2$, $SO_2N(R_{14})_2$, CO_2R_{14}, SO_3R_{14}, $N(R_{14})COR_{14}$, $CON(R_{14})_2$, or $N(R_{14})CON(R_{14})_2$;

wherein R_7 is H, branched or unbranched C_1-C_6 alkyl, branched or unbranched C_2-C_6 alkenyl or alkynyl, C_3-C_7 cycloalkyl, aryl, aryl-(C_1-C_6)-alkyl, CO_2R_{14}, $CON(R_{14})_2$,

substituted C_1-C_6 alkyl, substituted aryl, wherein the substituent is $N(R_{14})_2$, halogen, OR_{14} or SR_{14};

wherein R_8 is H or CH_3;

wherein R_{10} is H or F;

wherein R_{11} is H, F, Cl, Br, I, CN, branched or unbranched C_1- C_6 alkyl or alkoxy;

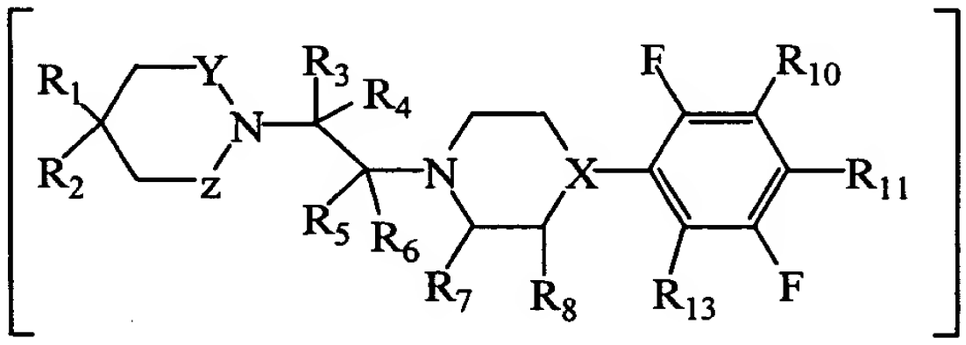
wherein R_{13} is H or F;

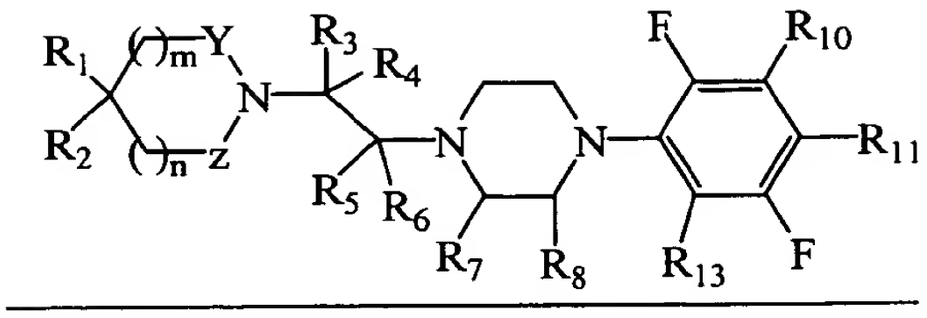
and wherein R_{14} is independently H or branched or unbranched C_1-C_6 alkyl.—-

--14.(Amended) The compound of claim 16, wherein the compound comprises the (+) enantiomer.—

--15.(Amended) The compound of claim 16, wherein the compound comprises the (-) enantiomer.--

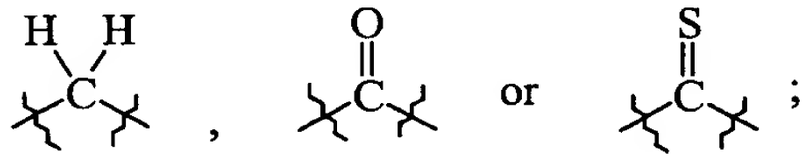
--16.(Amended) A compound [of claim 13 wherein the compound has] having the structure:





wherein each m and n is independently an integer from 0 to 2;

wherein each Y and Z is independently



wherein R_1 and R_2 (i) are independently H, branched or unbranched C_1-C_6 alkyl or alkoxy, branched or unbranched C_2-C_6 alkenyl or alkynyl, branched or unbranched C_1-C_6 hydroxyalkyl, hydroxy, substituted or unsubstituted aryl or aryl-(C_1-C_6)-alkyl, or substituted or unsubstituted heteroaryl or heteroaryl-(C_1-C_6)-alkyl, wherein the substituent if present is a halogen, CN, nitro, hydroxy, branched or unbranched C_1-C_6 alkyl or alkoxy group, or branched or unbranched C_2-C_6 alkenyl or alkynyl group; or (ii) taken together form a substituted or unsubstituted cycloalkyl ring containing 3-10 carbons, wherein the substituent if present is a branched or unbranched C_1-C_6 alkyl group or branched or unbranched C_2-C_6 alkenyl or alkynyl group;

wherein R_3 is H, branched or unbranched C_1-C_6 alkyl, branched or unbranched C_2-C_6 alkenyl or alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkylalkyl, aryl, heteroaryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl, substituted C_1-C_6 alkyl, substituted C_3-C_7 cycloalkyl, substituted aryl,

substituted heteroaryl, substituted aryl-(C_1-C_6)-alkyl, or substituted heteroaryl-(C_1-C_6)-alkyl, wherein the substituent if present is a halogen, CN, nitro, C_1-C_6 alkyl, OR_{14}, SR_{14}, $N(R_{14})_2$, $SO_2N(R_{14})_2$, CO_2R_{14}, SO_3R_{14}, $N(R_{14})COR_{14}$, $CON(R_{14})_2$, or $N(R_{14})CON(R_{14})_2$;

wherein R_4 is H or CH_3;

wherein R_5 is H, branched or unbranched C_1-C_6 alkyl, branched or unbranched C_2-C_6 alkenyl or alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkylalkyl, aryl, heteroaryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl, substituted C_1-C_6 alkyl, substituted C_3-C_7 cycloalkyl, substituted aryl, substituted heteroaryl, substituted aryl-(C_1-C_6)-alkyl, or substituted heteroaryl-(C_1-C_6)-alkyl, wherein the substituent if present is a halogen, CN, nitro, C_1-C_6 alkyl, OR_{14}, SR_{14}, $N(R_{14})_2$, $SO_2N(R_{14})_2$, CO_2R_{14}, SO_3R_{14}, $N(R_{14})COR_{14}$, $CON(R_{14})_2$, or $N(R_{14})CON(R_{14})_2$;

wherein R_6 is H, branched or unbranched C_1-C_6 alkyl, branched or unbranched C_2-C_6 alkenyl or alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkylalkyl, aryl, heteroaryl, aryl-(C_1-C_6)-alkyl, heteroaryl-(C_1-C_6)-alkyl, substituted C_1-C_6 alkyl, substituted C_3-C_7 cycloalkyl, substituted aryl, substituted heteroaryl, substituted aryl-(C_1-C_6)-alkyl, or substituted heteroaryl-(C_1-C_6)-alkyl, wherein the substituent if present is a halogen, CN, nitro, C_1-C_6 alkyl, OR_{14}, SR_{14}, $N(R_{14})_2$, $SO_2N(R_{14})_2$, CO_2R_{14}, SO_3R_{14}, $N(R_{14})COR_{14}$, $CON(R_{14})_2$, or $N(R_{14})CON(R_{14})_2$;

wherein R_7 is H, branched or unbranched C_1-C_6 alkyl, branched or unbranched C_2-C_6 alkenyl or alkynyl, C_3-C_7 cycloalkyl, aryl, aryl-(C_1-C_6)-alkyl, CO_2R_{14}, $CON(R_{14})_2$,

substituted C_1-C_6 alkyl, substituted aryl, wherein the substituent is $N(R_{14})_2$, halogen, OR_{14} or SR_{14};

wherein R_8 is H or CH_3;

wherein R_{10} is H or F;

wherein R_{11} is H, F, Cl, Br, I, CN, branched or unbranched C_1- C_6 alkyl or alkoxy;

wherein R_{13} is H or F;

and wherein R_{14} is independently H or branched or unbranched C_1-C_6 alkyl.—-

--22. (Amended) A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim [13] 16 and a pharmaceutically acceptable carrier.--

--29. (Amended) A pharmaceutical composition obtained by combining a therapeutically effective amount of [a] the compound of claim [13] 16 and a pharmaceutically acceptable carrier.—

--30. (Amended) A process for making a pharmaceutical composition comprising combining[a therapeutically effective amount of [a] the compound of claim [13] 16 and a pharmaceutically acceptable carrier.—-

--32. (Amended) A method of treating a subject afflicted with a disease which is susceptible to treatment by antagonism of the human α_{1d} adrenergic receptor which comprises administering to the subject an amount of the

compound of claim [13] 16 effective to treat the disease.--

--33. (Amended) A method of treating a subject afflicted with hypertension which comprises administering to the subject an amount of the compound of claim [13] 16 effective to treat the disease.--

--34. (Amended) A method of treating a subject afflicted with Raynaud's disease which comprises administering to the subject an amount of the compound of claim [13] 16 effective to treat the disease.--

--36. (Amended) A method of treating a subject afflicted with urinary incontinence which comprises administering to the subject an amount of the compound of claim [13] 16 effective to treat the disease.--